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| 10/068,137  | 02/06/2002  | Danilo Porro         | 2027.547096/RFE<br>(2005470) | 8385             |
| 23720   | 7590        | 11/26/2004           | EXAMINER                     |                  |
| WILLIAMS, MORGAN & AMERSON, P.C.<br>10333 RICHMOND, SUITE 1100<br>HOUSTON, TX 77042 |             |                      | KERR, KATHLEEN M             |                  |
|   |             |                      | ART UNIT                     | PAPER NUMBER     |
|   |             |                      | 1652                         |                  |

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

### Application No.

10/068,137

### Applicant(s)

PORRO ET AL.

### Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 35-43 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 35-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 4/22/04.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action, a non-final rejection (mailed on December 30, 2003), Applicants filed a response and amendment received on March 31, 2004. Said amendment amended Claims 35 and 38-41. Thus, Claims 35-43 are pending in the instant Office action and will be examined herein.

The Examiner notes that Claim 43 (filed by Applicant as Claim 45, but this was misnumbered as previously noted) was not previously examined; this was an oversight by the Office on first action as Claim 43 was filed as a preliminary amendment that had not been matched with the file.

### ***Priority***

2. As previously noted, the instant application is granted the benefit of priority for the foreign application MI97A002080 filed on September 12, 1997 and International Application No. PCT/EP98/05758 filed on September 11, 1998. The instant application is also granted the benefit of the parent application 09/508,277 filed on June 29, 2000, now USPN 6,429,006.

### ***Information Disclosure Statement***

3. The information disclosure statement filed on April 22, 2004 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion

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which caused it to be listed. The following references were not considered for the reasons described below:

- a) B7 is a duplicate of B4.
- b) C2 and C6, no copy was filed; the Abstract received is insufficient unless only the abstract is cited in the IDS.
- c) C3 is an incomplete citation without a source listed.
- d) C8-C10 must be listed under U.S. patent documents as U.S. Patent Application Publications.
- e) C11 has been considered but is crossed through since search report listings are not printed on the face of patents. Moreover, the search report filed is not the search report from the international prosecution of the instant application.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

#### ***Compliance with the Sequence Rules***

- 4. By virtue of Applicant's amendment, the instant application now fully complies with the sequence rules.

#### ***Withdrawn - Objections to the Specification***

- 5. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicant's amendment to the title.
- 6. Previous objection to the specification for lacking appropriate and updated continuity data in the first paragraph is withdrawn by virtue of Applicant's amendment.
- 7. Previous objection to the specification for having confusing stray marks is withdrawn by virtue of Applicant's amendment. Moreover, the Examiner agrees that this amendment is not

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new matter, as one of skill in the art would have readily understood the meaning of said marks and the changes to the data table required.

***Maintained - Objections to the Specification***

8. Previous objection to the specification for containing citations of internet addresses in an improper format is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the amendment has obviated the objection; the Examiner disagrees. Examples of proper internet citations are found in M.P.E.P. § 707.05(e), see specifically Example 5.

Moreover, citing post-filing date retrieval dates, as found in the amendment, are confusing. Was the pre-filing date sequence used? Has the sequence been updated since so that this sequence retrieved on February 16, 2004 might be different? Due to the well-known nature of GenBank sequences, the Examiner suggests removal of the internet address entirely from the specification, wherein the requirements of citing an internet web site would no longer apply.

***New - Objections to the Specification***

9. The amendment filed March 31, 2004 is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

- a) The amendment to page 28 that includes "reporting a sequence ...(1991)".
- b) The amendment to page 29 that includes "reporting a sequence ...supra".
- c) The amendment to page 32 that includes "reporting a sequence ...below".
- d) The amendment to page 40 that includes "reporting a sequence ...(1998)".

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While this information is implied by the disclosure of the GenBank accession numbers in each case, said accession numbers are not incorporated by reference and, thus, all their text cannot be inserted into the specification without new matter considerations.

Applicant is required to cancel the alleged new matter in the reply to this Office Action or to cite clear support (page and line number) in the specification as originally filed for the amendment.

***Withdrawn - Claim Objections***

10. Previous objection to Claim 41 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant's amendment.

***Withdrawn - Claim Rejections - 35 U.S.C. § 112***

11. Previous rejections of Claims 35-42 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant's amendment.

12. Previous rejection of Claims 38-40 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant's amendment.

13. Previous rejection of Claims 35-42 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of producing high yields of lactic acid using yeast strains with reduced pyruvate decarboxylase activity and optionally reduced pyruvate dehydrogenase activity, does not reasonably provide enablement for methods of producing high yields of lactic acid using yeast strains with reduced ethanol

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production ability via some other structural feature is withdrawn by virtue of Applicant's amendment adding this feature (albeit in function [not structural] form) to the claims..

***Maintained - Claim Rejections - 35 U.S.C. § 112***

14. Previous rejection of Claims 35-42 (added Claim 43) under 35 U.S.C. § 112, first paragraph, new matter, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that the upper limit of 1.0 gram lactic acid per gram carbon source is "inherent in the recited processes". Firstly, the Examiner disagrees. No evidence of complete conversion to lactic acid is found. Secondly, nowhere in the specification as originally filed did Applicant envision this scope. As previously noted,

"While the specification describes the invention using yeast with high "even higher yields (>80% g/g)" (see page 5, line 20), the Examiner can find no support for any claimed range except, perhaps, in the Examples. In Table 3B and Table 7, *Kluyveromyces* BM3-12D[pLAZ10] produces as high as 75.7%, 85.4% and 88.1% yield of lactose from glucose. In Table 3B, *Saccharomyces* CENPK113ΔPDC2[pLC5-KanMX] and CENPK113ΔPDC1, Δ5, Δ6[pLC5-KanMX] have 54.9 and 50% yields of lactose from glucose, respectively. In Table 6, *Kluyveromyces* PMI/C1[pEPL2], under extended fermentation (137 hours) produces 59% yield. Nowhere is 90% or 100% achieved. Thus, the range of 50-100% is not supported in the specification as originally filed."

Thus, the instant rejection is maintained.

The Examiner comments for the record that the new matter in question was filed on the day of filing of the instant application. As such, it can be considered part of the originally filed application if it were an original filing, but that is not the case here since what is filed is a divisional application related to an application filed on June 29, 2000. Since the "preliminary" amendment was filed after the effective filing date of June 29, 2000, it must be considered for new matter in the instant case.

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15. Previous rejection of Claims 35-42 (added Claim 43) under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for producing particular levels of lactate at particular pHs, does not reasonably provide enablement for producing 100% lactate from glucose at infinitely low pHs (see Claims 38-40) is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the working examples provided that produce up to 0.881 g/g yield enable 1.0 g/g yield (complete conversion of the carbon source to lactic acid) because routine experimentation of simple optimization would achieve such high yields. The Examiner disagrees. The specification is replete with examples of optimization procedures, yet 100% yield has not been achieved. No direction as to what other optimization techniques to try has been offered. And as previously noted, it is wholly unpredictable as to whether or not 100% yield can be achieved.

Applicant also argues that a skilled artisan would avoid toxic pH levels despite their being included in the claimed scope. While inoperative embodiments are permissible within the claimed scope, however, for Claim 38 reciting an initial pH limitation, this pH value must remain high (well above toxic levels) because the pH will decrease during fermentation. In fact, the initial pH's used in the examples of the instant specification are around 5.7. Therefore, for Claim 38, there appears to be more inoperative initial pH's than operative. Similar arguments can be made for Claims 39 and 40.

For all these reasons, the instant claims are not enabled to the full extent of their scope.



*New - Claim Rejections - 35 U.S.C. § 112*

16. Claims 35-43 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using yeast having deleted copies of their endogenous pyruvate decarboxylase or pyruvate dehydrogenase genes so as to reduce the activity of these enzymes in the yeast, does not reasonably provide enablement for methods using yeast having these enzymes' activities reduced by other means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To produce yeast strains for use in the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

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breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The specification teaches using yeast strains with deleted pyruvate decarboxylase or pyruvate dehydrogenase genes (see Tables B and C). The specification also teaches that

“The term “reduced pyruvate decarboxylase activity” means either a decreased concentration of enzyme in the cell or **reduced** or no specific **catalytic activity** of the enzyme.

The term “reduced pyruvate dehydrogenase activity” means either a decreased concentration of enzyme in the cell or **reduced** or no specific **catalytic activity** of the enzyme.” (emphasis added, from page 7 of the specification)

The specification provides no means for reducing (not deleting) the catalytic activity of these enzymes. Such reduction would require alteration (not obliteration) of the endogenous promoter or replacement of the endogenous encoding genes with genes encoding mutant enzymes having lower catalytic activity. The state of the art is silent on this subject. The specification provides no examples or guidance for the achievement of such reduced activity. It is wholly unpredictably to be able to produce such yeast mutants based on the lack of examples in the specification and the art. Thus, the instant claims are not enabled to the full extent of their scope.

#### ***Closest Prior Art***

17. Reiterated from the previous action, the following is a description of related prior art:

- a) Porro *et al.* (1995 – see IDS) teach *S. cerevisiae* GRF18 transformed with a bovine LDH gene can produce 50-70% yield lactic acid when the growth media carbon source is manipulated (see page 296, right column). However, GRF18 lacks the reduced ethanol production limitation. Porro *et al.* also teach the desire to reduce ethanol production in yeast harboring an LDH gene for the production of lactic acid. Porro *et al.* attempt this combination by transforming *S. cerevisiae* YSH 5.127-17 (a deleted *pdcl*, *pdcs*, and *pdcs* yeast strain) with a bovine LDH gene; however, the lactate production is “low” and not reported (see page 296, left column).

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Porro's using YSH 5.127-17 is very similar to Applicants' using *S. cerevisiae* CENPK113PDCΔ1,Δ5,Δ6[pLC5-KanMX] to produce a 50% lactate yield, the difference being that Applicants' LDH gene is from *L. casei* and said gene is on an integrating vector as opposed to the replicative vector with bovine LDH of Porro *et al.* Thus, a case for inherency cannot be made that the teachings of Porro *et al.* would produce a 50% yield of lactate.

### ***Conclusion***

18. Claims 35-43 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr  
Primary Examiner  
Art Unit 1652

November 21, 2004